[Chem. Pharm. Bull. 32(11)4328—4339(1984)]

# Novel Synthesis of Optically Pure Anthracyclinone Intermediates by the Use of Microbial Asymmetric Reduction with Fermenting Baker's Yeast[1)]

KATSUMI TAMOTO and SHIRO TERASHIMA*,[2)]

*Faculty of Pharmaceutical Sciences, University of Tokyo, 7-3-1, Hongo, Bunkyo-ku, Tokyo 113, Japan*

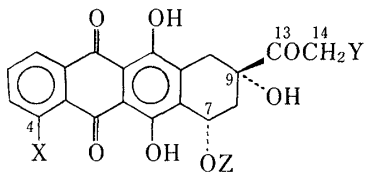
(Received March 6, 1984)

Microbial reduction of the racemic α-hydroxy ketones ((±)-**3a**, **b**) with fermenting baker's yeast was found to afford diastereomeric mixtures of the *vicinal*-diols ((−)-**4a**, **b**) and ((+)-**5a**, **b**) in 90 and 91% yields, respectively. Separation of these diastereomers was readily accomplished by fractional recrystallization, giving pure (−)-**4a**, **b** and mixtures of (−)-**4a**, **b** and (+)-**5a**, **b**. Oxidation of these samples furnished optically pure anthracyclinone intermediates ((*R*)-(−)-**3a**, **b**) and their partially optically active antipodes ((*S*)-(+)-**3a**, **b**). The undesired enantiomers ((*S*)-(+)-**3a**, **b**) and *vicinal*-diols((+)-**5a**, **b**) could be recycled to (±)-**3a**, **b** and the prochiral ketones (**6a**, **c**) by racemization with *p*-toluenesulfonic acid and oxidative cleavage with sodium metaperiodate, respectively.

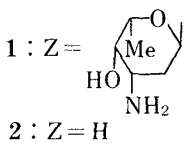
Another important optically pure anthracyclinone intermediate ((*R*)-(−)-**3c**) was prepared from (*R*)-(−)-**3a**, **b** according to the reported method.

**Keywords**——α-hydroxy ketone; microbial reduction; anthracycline; optically pure anthracyclinone; 4-demethoxyanthracycline; optically pure 4-demethoxyanthracyclinone; baker's yeast; oxidation; racemization; *vicinal*-diol

The anthracycline antibiotics, adriamycin (**1a**) and daunorubicin (**1b**), are of great current interest in view of their activity against many types of human cancers.[3-5)] Various undesirable side effects, the most notable and serious of which is dose-related cardiotoxicity, restricts the utility of **1a**, **b** for cancer chemotherapy,[3-5)] but extensive studies involving the synthesis and testing of analogs of **1a**, **b** have culminated in the development of unnatural 4-demethoxyanalogs, 4-demethoxyadriamycin (**1c**) and 4-demethoxydaunorubicin (**1d**), which could show better therapeutic indices than natural **1a**, **b**.[3b,e,4,6,7)]



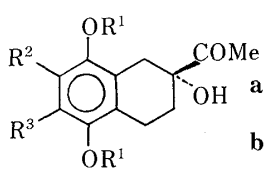
| | X | Y |
|---|---|---|
| **a** | OMe | OH |
| **b** | OMe | H |
| **c** | H | OH |
| **d** | H | H |



1 : Z=



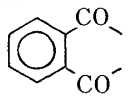
2 : Z=H



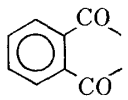
(*R*)-(−)-**3**

**a** : $R^1$=Me, $R^2$=$R^3$=H

**b** : $R^1$=Me, $R^2$, $R^3$=



**c** : $R^1$=H, $R^2$, $R^3$=



Recently, the optically active α-hydroxy ketones ((*R*)-(−)-**3a**—**c**) have attracted much attention as versatile key synthetic intermediates from which optically pure natural and unnatural anthracyclinones (**2a**—**d**), the aglycones of **1a**—**d**, can be elaborated.[6,7)] Synthesis

of optically pure (*R*)-(−)-**3a** was achieved originally by optical resolution of the corresponding racemic modification[6,7a,c,d] and later by asymmetric synthesis employing a halolactonization reaction[8,9] or reduction with chiral hydride.[10] The tetracyclic ketones ((*R*)-(−)-**3b**, **c**), which are directly convertible to optically pure **2c**, **d**, can be synthesized by Friedel–Crafts acylation of (*R*)-(−)-**3a**.[6,7,10] With the importance of unnatural **1c**, **d**, various methods featuring direct optical resolution of the racemic tetracyclic ketone ((±)-**3c**)[11,12] and kinetic resolution by the use of asymmetric epoxidation,[13] have been developed for producing optically active (*R*)-(−)-**3c**. Recently, a novel synthesis of optically pure **2d** has also been achieved by applying an asymmetric Diels–Alder reaction[14] or optical resolution[15] in the key synthetic step.

In view of the importance of (*R*)-(−)-**3a**—**c** in the synthesis of optically pure **2**, further attempts were made to develop a simple and efficient method to produce optically pure (*R*)-(−)-**3a**—**c**. We have now found that optically pure (*R*)-(−)-**3a**—**c** can be readily prepared by the optical resolution of (±)-**3a**, **b** by means of microbial asymmetric reduction followed by oxidation (for (*R*)-(−)-**3a**—**c**) and demethylation (for (*R*)-(−)-**3c**). Since the undesired enantiomers and distereomers can be recycled to reusable compounds, the overall process is anticipated to have a similar efficacy to that of asymmetric synthesis.

This report describes in detail a novel preparation of (*R*)-(−)-**3a**—**c** accomplished by the use of microbial asymmetric reduction with fermenting baker's yeast.[1]

## Results and Discussion

It is well known that microorganisms including fermenting baker's yeast reduce various structural types of ketones in a highly stereoselective manner to afford chiral alcohols.[16] This novel asymmetric transformation has been successfully applied to optical resolution of prostaglandin[17,18] and macrolide[19] intermediates in addition to asymmetric synthesis of optically active secondary alcohols which can be used for preparing biologically active natural products.[16b-e] In the course of our studies on the synthesis of optically active **2a**—**d**, we have found that asymmetric reduction with fermenting baker's yeast, a well-known and simple microbial reduction,[16] is quite effective for resolving the racemic α-hydroxy ketones ((±)-**3a**, **b**) which are the key intermediates of anthracyclinone synthesis.[6-8,10,11,20]

Thus, as shown in Chart 1, treatment of (±)-**3a**,[22-26] readily prepared from the β-tetralone (**6a**)[27] *via* two synthetic schemes[25] (see Experimental), with actively fermenting baker's yeast (*Saccharomyces cerevisiae*) (Sigma YSC-1) followed by extractive isolation and separation with a short silica gel column was found to give a mixture of the diastereomeric *vicinal*-diols ((−)-**4a** and (+)-**5a**), $[\alpha]_D^{20}$ +1.4° (ethanol), in 90% yield. The ratio of (−)-**4a** to (+)-**5a** was determined to be 48 : 52 by HPLC. Three recrystallizations of the mixture from benzene–hexane gave pure (−)-**4a**, $[\alpha]_D^{20}$ −50.3° (ethanol), in 32% yield (63% based on (*R*)-(−)-**3a** present in (±)-**3a**). Concentration of the combined mother liquors from the recrystallizations afforded a crude mixture of (−)-**4a** and (+)-**5a** in 58% yield. The ratio of the two *vicinal*-diols was calculated as 18 : 82 from the optical purity of (*S*)-(+)-**3a** derived from this mixture (*vide infra*). Separation of (+)-**5a** from the mixture was similarly examined by repeated recrystallizations from benzene–hexane, giving a sample consisting of (−)-**4a** and (+)-**5a** in a ratio of 7 : 93 (determined by HPLC).

The *vicinal*-diol ((−)-**4a**) was confirmed to be identical with authentic (−)-**4a**, $[\alpha]_D^{20}$ −49.7° (ethanol), previously prepared by asymmetric reduction of 2-acetyl-5,8-dimethoxy-3,4-dihydronaphthalene followed by epoxidation and reduction,[10] by means of spectral and chromatographic comparisons and mixed melting point measurement. The *vicinal*-diols ((−)-**4a** and (+)-**5a**) were converted to the dioxolane derivatives ((+)-**7** and (+)-**8**), respectively, to unambiguously determine their structures. The former dioxolane ((+)-**7**) showed its $C_5$-

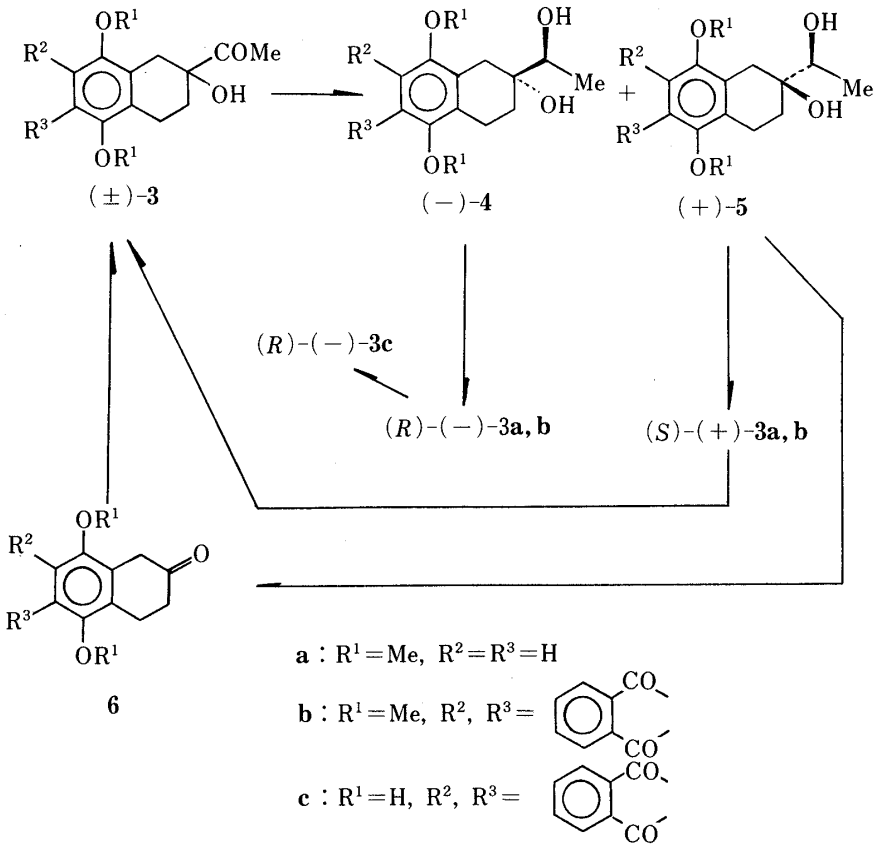



Chart 1

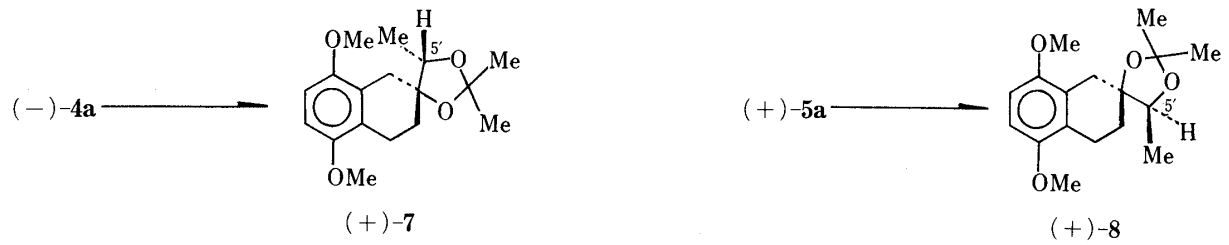



Chart 2

methyl signal at higher field (1.15 ppm) than that for the latter compound ((+)-**8**) (1.26 ppm). This spectral feature clearly demonstrates that the $C_{5'}$-methyl group of (+)-**7** is in closer proximity to the aromatic ring than that of (+)-**8**. From this result, together with the result of oxidation, which gave (*R*)-(−)- and (*S*)-(+)-**3a** from (−)-**4a** and (+)-**5a**, respectively, (−)-**4a** and (+)-**5a** were definitely established as having (1′*S*, 2*R*) and (1′*S*, 2*S*) configurations.

Next, in order to establish the stereoselectivity of the reduction of (±)-**3a**, optically pure (*R*)-(−)- and (*S*)-(+)-**3a** derived from (−)-**4a** and (+)-**5a** (*vide infra*) were separately subjected to microbial reduction under the same conditions as for (±)-**3a**. Since (−)-**4a** (or (+)-**5a**) was obtained as a sole reduction product (determined by HPLC), it appeared evident that the reduction of (±)-**3a** proceeds highly stereoselectively, only giving the diastereomeric mixture of (−)-**4a** and (+)-**5a**. This demonstrates that the steric course of the reduction of (±)-**3a** followed the so-called Prelog rule (selective formation of an (*S*)-alcohol) proposed for

the asymmetric reduction of prochiral ketones with yeast,[16a] and that the asymmetric center involved in (±)-**3a** does not affect the steric course of the microbial reduction.

Oxidation of (−)-**4a** with dimethyl sulfoxide–sulfur trioxide·pyridine complex–triethylamine according to the reported method,[10,28] gave optically pure (*R*)-(−)-**3a**, $[\alpha]_D^{20}$ −46.3° (chloroform), in 90% yield. Similarly, optically pure (*S*)-(+)-**3a**, $[\alpha]_D^{20}$ +46.7° (chloroform), could be prepared from (+)-**5a** contaminated with a small amount of (−)-**4a** (*ca.* 7%) by similar oxidation followed by repeated recrystallizations. Treatment of the mixture of (−)-**4a** and (+)-**5a** (18:82) with the same oxidizing reagent afforded optically active (*S*)-(+)-**3a**, $[\alpha]_D^{20}$ +30.2° (chloroform), 65% ee, in 72% yield.

In order to improve the efficacy of the process, conversion of a mixture of (−)-**4a** and (+)-**5a** to **6a** and racemization of partially optically active (*S*)-(+)-**3a** were next examined. The former transformation could be readily achieved by treating the crude mixture of (−)-**4a** and (+)-**5a** with sodium metaperiodate in aqueous acetone, affording **6a** in 99% yield. However, racemization of (*S*)-(+)-**3a** was found to be quite refractory, though the preparation of (*R*)-(−)-**3b**, **c** from (*R*)-(−)-**3a** by Friedel–Crafts acylation in the presence of aluminum chloride had already been reported to occur with partial racemization.[10]

TABLE I. Racemization of Partially Optically Active (*S*)-(+)-2-Acetyl-5,8-dimethoxy-1,2,3,4-tetrahydro-2-naphthol ((*S*)-(+)-**3a**)[a]

| Run | Reaction conditions for racemization | | | | | Recovered (*S*)-(+)-**3a** | | |
|---|---|---|---|---|---|---|---|---|
| | Acid used for the racemization | | Solv. (v/v ratio) | Temp. (°C) | Time (h) | Recovery Yield (%)[b] | Racemization (%)[c] | Racemization efficiency (%)[d] |
| | Acid | eq[e] | | | | | | |
| 1 | $HClO_4$[f] | 115 | $CH_3COOH$ | 110 | 2 | 0 | — | — |
| 2 | $HClO_4$[g] | 3.8 | Dioxane | 110 | 5 | 97 | 3 | 3 |
| 3 | HCl[h] | 150 | $CH_3COOH$ | 110 | 5.3 | 66 | 46 | 30 |
| 4 | $CF_3COOH$ | 220 | $CF_3COOH$ | 72 | 3 | 100 | 3 | 3 |
| 5 | $CF_3SO_3H$ | 1 | $CF_3COOH$ | 70 | 2.5 | 26 | 90 | 23 |
| 6 | $CF_3SO_3H$ | 21 | $CF_3COOH$–$H_2O$ (5:2) | 100 | 2 | 66 | 55 | 36 |
| 7 | TsOH[i] | 5 | DMSO | 160 | 1 | 79 | 10 | 8 |
| 8 | TsOH[i] | 10 | $C_6H_6$ | 80 | 20 | 0 | — | — |
| 9 | TsOH[i] | 17.4 | $CH_3COOH$ | 110 | 20 | 0 | — | — |
| 10 | TsOH[i] | 10 | $CH_3COOH$–$H_2O$ (3:2) | 150[j] | 1 | 98 | 17 | 17 |
| 11 | TsOH[i] | 10 | $CH_3COOH$–$H_2O$ (3:2) | 110 | 20 | 89 | 41 | 36 |
| 12 | TsOH[i] | 70 | $CH_3COOH$–$H_2O$ (7:4) | 110 | 20 | 74 | 87 | 64 |

*a*) All reactions were performed using (*S*)-(+)-**3a** (15—75 mg (0.06—0.30 mmol), $[\alpha]_D^{20}$ +26.3°—+33.1° (*c*=0.88—1.01, $CHCl_3$), 57—71% ee) derived from a mixture of (−)-**4a** and (+)-**5a**.
*b*) Calculated based on (*S*)-(+)-**3a** purified by PTLC ($SiO_2$, benzene–ethyl acetate, 6:1).
*c*) Calculated by means of the following equation: racemization (%)=[1−(optical purity of racemized (*S*)-(+)-**3a**)/(optical purity of starting (*S*)-(+)-**3a**)]×100.
*d*) Calculated by means of the following equation: racemization efficiency (%)=racemization (%)×recovery yield (%)÷100.
*e*) Equivalent to (*S*)-(+)-**3a** used.
*f*) 60% perchloric acid was used.
*g*) 20% perchloric acid was used.
*h*) Conc. hydrochloric acid was used.
*i*) *p*-Toluenesulfonic acid monohydrate was used.
*j*) The reaction mixture was heated in a sealed tube.

Several representative results on the racemization of partially optically active (*S*)-(+)-**3a** by using various acids are summarized in Table I.

Although no clear general trend is apparent from the tabulated data, it is evident that sulfonic acids such as trifluoromethanesulfonic acid and *p*-toluenesulfonic acid generally give better results than mineral acids and carboxylic acids (see Table I, runs 1—4 and 5, 6, 10—12), and that acetic acid and trifluoroacetic acid are solvents of choice (see Table I, runs 5—8 and 10—12). The presence of water in the racemization medium is absolutely necessary to avoid decomposition of (*S*)-(+)-**3a** (see Table I, runs 5, 6 and 9—12).

It was finally found that, when a mixture of partially optically active (*S*)-(+)-**3a**, $[\alpha]_D^{20}$ +30.2° (chloroform), 65% ee, and *p*-toluenesulfonic acid monohydrate (70 eq) in aqueous acetic acid was heated at 110 °C for 20 h, almost wholly racemized (*S*)-(+)-**3a**, $[\alpha]_D^{20}$ +3.9° (chloroform), 8% ee, 87% racemization (see Table I, footnote *d*)), could be obtained in 74% yield (Table I, run 12). Recrystallization of this sample from cyclohexane gave (±)-**3a** in 58% yield based on (*S*)-(+)-**3a**. Recovered **6a** and (±)-**3a** can be utilized again for the preparation of (±)-**3a** and for the microbial asymmetric reduction, respectively.

The racemization mechanism of (*S*)-(+)-**3a** is of interest because the racemized asymmetric center is involved in an α,α-disubstituted-α-hydroxy ketone system. Detailed mechanistic studies, which are the subject of the accompanying paper,[29] have indicated that the racemization might proceed through the ring-expanded seven-membered α-hydroxy ketones.

Next, application of the overall process to the preparation of (*R*)-(−)-**3b**, **c** was attempted. While (±)-**3c**, prepared from (±)-**3a** by the reported procedure,[7b,e,10b,26a] was found to be useless for the microbial reduction due to its extremely low solubility in an aqueous reduction medium, treatment of (±)-**3b** produced by methylation of (±)-**3c**,[10b] with fermenting baker's yeast in a mixture of water and dimethyl sulfoxide (10 : 1),[30] successfully afforded a mixture of (−)-**4b** and (+)-**5b**, $[\alpha]_D^{20}$ −2.9° (*N*,*N*-dimethylformamide), in 91% yield. Repeated recrystallizations from benzene gave pure (−)-**4b**, $[\alpha]_D^{20}$ −39.0° (*N*,*N*-dimethylformamide), in 19% yield (37% based on (*R*)-(−)-**3b** involved in (±)-**3b**). Concentration of the combined mother liquors from the recrystallizations afforded a crude mixture of (−)-**4b** and (+)-**5b**, $[\alpha]_D^{20}$ +9.2° (*N*,*N*-dimethylformamide), in 72% yield. The ratio of the two *vicinal*-diols was determined to be 39 : 61 from the optical purity of (*S*)-(+)-**3b** derived from this sample. Although (+)-**5b** could not be isolated in a pure state, the sign of the optical rotation for **5b** was deduced from the optical rotation of the mixture and the ratio of (−)-**4b** to (+)-**5b**. The diastereomeric *vicinal*-diols ((−)-**4b** and (+)-**5b**) were also presumed to have (1′*S*,2*R*) and (1′*S*,2*S*) configurations, respectively, based on the results of the oxidation of (−)-**4b** and (+)-**5b** (*vide infra*) and by assuming that the microbial reduction of (±)-**3b** is similar to that of (±)-**3a**. The result of separate microbial reduction of optically pure (*R*)-(−)-**3b** also suggests that the crude product from (±)-**3b** consists solely of the two *vicinal*-diols ((−)-**4b** and (+)-**5b**).

Oxidation of (−)-**4b** and the mixture of (−)-**4b** and (+)-**5b** in the same manner as described for (−)-**4a** readily afforded optically pure (*R*)-(−)-**3b**, $[\alpha]_D^{20}$ −23.4° (chloroform), and partially optically active (*S*)-(+)-**3b**, $[\alpha]_D^{20}$ +5.2° (chloroform), 22% ee, in 86 and 88% yields, respectively.

Since a complex mixture of products was obtained when the crude mixture of (−)-**4b** and (+)-**5b** was directly subjected to periodate oxidation,[31] oxidative cleavage was attempted using a mixture of the demethylated *vicinal*-diols (**4c** and **5c**). Thus, successive treatments of the mixture of (−)-**4b** and (+)-**5b** with aluminum chloride[10b,22] and with sodium metaperiodate gave **6c** in 71% overall yield. The tetracyclic ketone (**6c**) has been reported to be usable for the preparation of (±)-**3b**, **c**.[32]

In contrast to the case of (*S*)-(+)-**3a**, racemization of partially optically active (*S*)-(+)-

**3b** proceeded with complete demethylation. Methylation[10b] of the reaction product gave extensively racemized (*S*)-(+)-**3b**, $[\alpha]_D^{20}$ +1.8° (chloroform), 8% ee, 64% racemization (see Table I, footnote *c*)), in 70% yield. This was recrystallized from benzene–cyclohexane, affording (±)-**3b** in 50% yield based on (*S*)-(+)-**3b**.

While the microbial reduction of (±)-**3c** failed due to the low solubility of (±)-**3c** as mentioned above, optically pure (*R*)-(−)-**3c**, $[\alpha]_D^{20}$ −90.0° (chloroform), could be prepared from (*R*)-(−)-**3a** by Friedel–Crafts acylation[7e,10b,26a] or from (*R*)-(−)-**3b** by demethylation.[10b,22] Although the former reaction proceeded with 18% racemization in accordance with a previous report,[10] repeated recrystallizations of partially optically active (*R*)-(−)-**3c** gave the optically pure sample.

With optically pure (*R*)-(−)-**3a**—**c** in hand, it became possible to synthesize optically active **2a**—**d**, especially optically pure **2c**, **d**, by employing the microbial asymmetric reduction with fermenting baker's yeast. The present reaction scheme seems to be practically useful, offering the advantages of operational simplicity, use of readily available cheap reagents such as baker's yeast, and efficient processes for recycling the undesired isomers.

## Experimental[33]

**(±)-2-Acetyl-5,8-dimethoxy-1,2,3,4-tetrahydro-2-naphthol ((±)-3a)**——a) Preparation of (±)-**3a** from **6a** *via* (±)-2-Ethynyl-5,8-dimethoxy-1,2,3,4-tetrahydro-2-naphthol: Addition of ethynylmagnesium bromide to **6a**[27] in THF, followed by hydration with HgO in aq $H_2SO_4$ according to the reported procedure,[10,24,25] gave (±)-**3a** in 65% overall yield. A sample recrystallized from $Et_2O$ showed mp 102—103 °C (lit.,[10] mp 100—101 °C; lit.,[22a] mp 100—102 °C).

b) Preparation of (±)-**3a** from **6a** *via* (±)-2-Hydroxy-5,8-dimethoxy-1,2,3,4-tetrahydronaphthalene-2-carboxylic Acid: Treatment of **6a**[27] with KCN and AcOH in $CHCl_3$, followed by acidic hydrolysis with conc. HCl according to the reported method,[23] gave (±)-2-hydroxy-5,8-dimethoxy-1,2,3,4-tetrahydronaphthalene-2-carboxylic acid. A pure sample was obtained by recrystallization from $C_6H_5Me$, mp 167—169 °C (lit.,[23] mp 169—170 °C).

Acetyl chloride (10 ml) was added to stirred MeOH (100 ml) below 0 °C and (±)-2-hydroxy-5,8-dimethoxy-1,2,3,4-tetrahydronaphthalene-2-carboxylic acid (5.0 g, 20 mmol) was added to the stirred acidic methanolic solution. After being heated at reflux for 5 h with stirring, the mixture was concentrated *in vacuo*. The residue was dissolved in $CH_2Cl_2$, washed successively with $H_2O$, satd. $NaHCO_3$, and $H_2O$, then dried. Filtration and concentration of the filtrate *in vacuo* gave crude (±)-methyl 2-hydroxy-5,8-dimethoxy-1,2,3,4-tetrahydronaphthalene-2-carboxylate as a solid (5.5 g, 98%). Recrystallization from MeOH gave a pure sample, mp 79—81 °C (lit.,[15b] mp 76.5—77 °C).

A solution of sodium methylsulfinylcarbanide prepared from sodium hydride (50% oil dispersion) (12.0 g, 0.25 mol) and DMSO (100 ml) at 70—75 °C was diluted with THF (100 ml), then cooled below 5 °C. (±)-Methyl 2-hydroxy-5,8-dimethoxy-1,2,3,4-tetrahydronaphthalene-2-carboxylate (20.0 g, 75 mmol) was added to the solution of sodium methylsulfinylcarbanide in DMSO–THF prepared above, and the mixture was stirred at room temperature for 15 h. After being cooled in an ice bath, the mixture was diluted successively with satd. NaCl and conc. HCl, then extracted with $CH_2Cl_2$. The organic extracts were combined and washed successively with 5% HCl, $H_2O$, satd. $NaHCO_3$, and satd. NaCl. Filtration and concentration of the filtrate *in vacuo* gave an oily residue, which was crystallized by triturating with $Et_2O$. The crude (±)-5,8-dimethoxy-2-(methylsulfinyl)acetyl-1,2,3,4-tetrahydro-2-naphthol, which consists of two diastereomers due to the asymmetric sulfur atom, weighed 21.8 g (93%) and showed mp 115—137 °C. Fractional recrystallizations from EtOH gave analytical samples as two sorts of crystalline products.

mp 158—161 °C. IR $\nu_{max}^{KBr}$ $cm^{-1}$: 3350, 1710, 1480. NMR ($CDCl_3$) $\delta$: 1.5—2.1 (2H, m, $CH_2C\underline{H}_2C(OH)$), 2.69 (3H, s, $SOC\underline{H}_3$), 2.4—3.1 (4H, m, $ArC\underline{H}_2 \times 2$), 3.54 (1H, d, $J$=12 Hz, one of $C\underline{H}_2SO$), 3.72 and 3.75 (each 3H, two s, $OC\underline{H}_3 \times 2$), 4.56 (1H, s, O<u>H</u>), 4.67 (1H, d, $J$=12 Hz, one of $C\underline{H}_2SO$), 6.57 (2H, s, aromatic protons). *Anal.* Calcd for $C_{15}H_{20}O_5S$: C, 57.67; H, 6.45. Found: C, 57.45; H, 6.45.

mp 129—130 °C. IR $\nu_{max}^{KBr}$ $cm^{-1}$: 3240, 1705, 1480. NMR ($CDCl_3$) $\delta$: 1.6—2.1 (2H, m, $CH_2C\underline{H}_2C(OH)$), 2.70 (3H, s, $SOC\underline{H}_3$), 2.7—3.1 (4H, m, $ArC\underline{H}_2 \times 2$), 3.65 (1H, d, $J$=12 Hz, one of $C\underline{H}_2SO$), 3.72 and 3.75 (each 3H, two s, $OC\underline{H}_3 \times 2$), 4.40 (1H, s, O<u>H</u>), 4.59 (1H, d, $J$=12 Hz, one of $C\underline{H}_2SO$), 6.58 (2H, s, aromatic protons). *Anal.* Calcd for $C_{15}H_{20}O_5S$: C, 57.67; H, 6.45. Found: C, 57.63; H, 6.45.

Aluminum foil (4.24 g, 0.16 mol) was covered with 2% aq. $HgCl_2$ solution, and the mixture was kept standing at room temperature for 1 min. After removal of the aqueous layer by decantation, the formed aluminum amalgam was washed successively with $H_2O$, EtOH, and THF, then covered with THF (400 ml). (±)-5,8-Dimethoxy-2-(methylsulfinyl)-acetyl-1,2,3,4-tetrahydro-2-naphthol (20.0 g, 64 mmol) was added to a THF suspension of aluminum

amalgam, and the mixture was stirred at 50 °C for 3 h. After being cooled, the mixture was diluted with satd. NaCl, and extracted with EtOAc. The combined organic extracts were washed successively with 5% HCl, satd. $NaHCO_3$, and satd. NaCl. Filtration and concentration of the filtrate *in vacuo* gave an oily residue, which was triturated with iso-$Pr_2O$ to give (±)-**3a** (13.5 g, 84%), mp 101—103 °C. Recrystallization from EtOH gave a pure sample, mp 103—104 °C. The spectral IR and NMR and chromatographic thin layer chromatography (TLC) properties of this sample were identical with those of (±)-**3a** prepared in a).

**Reduction of (±)-2-Acetyl-5,8-dimethoxy-1,2,3,4-tetrahydro-2-naphthol ((±)-3a) with Baker's Yeast**——Preparation of (1′*S*,2*R*)-(−)-2-1′-Hydroxyethyl-5,8-dimethoxy-1,2,3,4-tetrahydro-2-naphthol ((−)-**4a**) and Its (1′*S*,2*S*)-(+)-Isomer ((+)-**5a**): Baker's yeast (*Saccharomyces cerevisiae*) (Sigma YSC-1) (17.5 g) was added to a solution of sucrose (25 g) in $H_2O$ (200 ml), and the suspension was stirred at 30—35 °C for 1 h. Powdered (±)-**3a** (1.0 g, 4.0 mmol) was added to the aqueous suspension, and the whole was stirred at the same temperature for 48 h. The reaction mixture was filtered through a pad of celite, and the collected mass was washed successively with EtOH (×3) and EtOAc (×2). The ethanolic filtrates were combined and concentrated *in vacuo* to give an oily residue, which was combined with the aqueous filtrate. The whole aqueous mixture was extracted first with the combined EtOAc washings, then with EtOAc. The organic extracts were combined and washed successively with $H_2O$ and satd. NaCl. Filtration and concentration of the filtrate *in vacuo* gave an oily residue (1.39 g), which was subjected to column chromatography ($SiO_2$ 30 g, $CH_2Cl_2$) to afford a mixture of (−)-**4a** and (+)-**5a** (980 mg, 90%). HPLC analysis showed that this sample contained (−)-**4a** and (+)-**5a** in a ratio of 48:52. The NMR spectrum of this sample exhibited two sets of doublets of equal intensity at 1.21 and 1.24 ppm ($J$=each 6 Hz). This also suggests that almost equal amounts of (−)-**4a** and (+)-**5a** are present in the crude mixture. Three recrystallizations from $C_6H_6$–$C_6H_{14}$ gave pure (−)-**4a** (295 mg, 32% (63% based on (*R*)-(−)-**3a** involved in (±)-**3a**)), mp 154—155 °C, $[\alpha]_D^{20}$ −50.3° ($c$=0.66, EtOH) (lit.,[10] mp 154—155 °C, $[\alpha]_D^{20}$ −49.7° ($c$=0.50, EtOH)). IR $\nu_{max}^{KBr}$ $cm^{-1}$: 3340, 1600, 1480, 1255, 1080. NMR ($CDCl_3$) $\delta$: 1.24 (3H, d, $J$=6 Hz, $CHC\underline{H}_3$), 1.4—2.1 (2H, m, $ArCH_2C\underline{H}_2$), 1.92 (1H, s, O<u>H</u>), 2.17 (1H, d, $J$=5 Hz, O<u>H</u>), 2.4—3.1 (4H, m, $ArC\underline{H}_2$ ×2), 3.73 and 3.75 (each 3H, two s, $OC\underline{H}_3$ ×2), 3.5—3.9 (1H, m, C<u>H</u>(OH)), 6.55 (2H, s, aromatic protons). These spectral data were identical with those reported.[10b] This sample showed no depression on mixed melting point measurement with an authentic sample,[10] mmp 154—155 °C. *Anal.* Calcd for $C_{14}H_{20}O_4$: C, 66.65; H, 7.99. Found: C, 66.71; H, 7.99.

Mother liquors from the repeated recrystallizations were combined and concentrated *in vacuo* to give a mixture of (−)-**4a** and (+)-**5a** (582 mg, 58%). The ratio of (−)-**4a** to (+)-**5a** was determined as 18:82 from the optical purity of (*S*)-(+)-**3a** derived from this sample.

Another lot of the mixture of (−)-**4a** and (+)-**5a** (420 mg), $[\alpha]_D^{20}$ +26.1° ($c$=0.69, EtOH), obtained by concentration of the combined mother liquors from the repeated recrystallizations, was recrystallized five times from $C_6H_6$–$C_6H_{14}$, giving almost pure (+)-**5a** (33 mg) as colorless crystals, mp 70—75 °C, $[\alpha]_D^{20}$ +41.1° ($c$=0.32, EtOH). The ratio of (−)-**4a** to (+)-**5a** in this sample was determined as 7:93 by HPLC analysis. IR $\nu_{max}^{KBr}$ $cm^{-1}$: 3360, 1475, 1250. NMR ($CDCl_3$) $\delta$: 1.21 (3H, d, $J$=6 Hz, $CHC\underline{H}_3$), 1.4—2.0 (2H, m, $ArCH_2C\underline{H}_2$), 2.23 (2H, br s, O<u>H</u> ×2), 2.6—2.9 (4H, m, $ArC\underline{H}_2$ ×2), 3.74 and 3.75 (each 6H, two s, $OC\underline{H}_3$ ×2), 3.6—3.9 (1H, m, C<u>H</u>(OH)), 6.55 (2H, s, aromatic protons). *Anal.* Calcd for $C_{14}H_{20}O_4$: C, 66.65; H, 7.99. Found: C, 66.94; H, 8.02.

**(+)-5,8-Dimethoxy-2′,2′,5′(*S*)-trimethyl-3,4-dihydrospiro[naphthalene-2(*R*)(1*H*),4′(*R*)-1,3-dioxolane] ((+)-7)**——A mixture of (−)-**4a** (mp 154—155 °C, $[\alpha]_D^{20}$ −49.9° ($c$=0.78, EtOH)) (100 mg, 0.40 mmol) and TsOH–$H_2O$ (7.5 mg, 0.04 mmol) in 2,2-dimethoxypropane (1 ml) was stirred at room temperature for 12 h. The reaction mixture was diluted with satd. $NaHCO_3$, and extracted with EtOAc. The combined organic extracts were washed with $H_2O$. Filtration and concentration of the filtrate *in vacuo*, followed by purification by PTLC ($SiO_2$, $C_6H_6$) gave (+)-**7** (103 mg, 89%). Recrystallization from $C_6H_{14}$ gave an analytical sample, mp 85—86 °C, $[\alpha]_D^{20}$ +6.1° ($c$=2.02, $CHCl_3$). IR $\nu_{max}^{KBr}$ $cm^{-1}$: 1475, 1375, 1245, 1160. NMR ($CDCl_3$) $\delta$: 1.15 (3H, d, $J$=6 Hz, $CHC\underline{H}_3$), 1.40 and 1.48 (each 6H, two s, $C(C\underline{H}_3)_2$), 1.55—2.2 (2H, m, $ArCH_2C\underline{H}_2$), 2.45—3.2 (4H, m, $ArC\underline{H}_2$ ×2), 3.79 (6H, two s, $OC\underline{H}_3$ ×2), 4.05 (1H, q, $J$=6 Hz, $C\underline{H}CH_3$), 6.62 (2H, s, aromatic protons). *Anal.* Calcd for $C_{17}H_{24}O_4$: C, 69.84; H, 8.27. Found: C, 69.84; H, 8.33.

**(+)-5,8-Dimethoxy-2′,2′,5′(*S*)-trimethyl-3,4-dihydrospiro[naphthalene-2(*S*)(1*H*),4′(*S*)-1,3-dioxolane]((+)-8)**——Treatment of (+)-**5a** (mp 65—75 °C, $[\alpha]_D^{20}$ +36.4° ($c$=0.79, EtOH)) (150 mg, 0.59 mmol) in the same manner as described for (−)-**4a** gave crude (+)-**8** (141 mg, 81%) after extractive isolation followed by purification by PTLC. Four recrystallizations of this sample from $C_6H_{12}$ gave an analytical sample, mp 107—108 °C, $[\alpha]_D^{20}$ +49.6° ($c$=1.70, $CHCl_3$). IR $\nu_{max}^{KBr}$ $cm^{-1}$: 1475, 1360, 1245, 1075. NMR ($CDCl_3$) $\delta$: 1.26 (3H, d, $J$=6 Hz, $CHC\underline{H}_3$), 1.38 and 1.45 (each 3H, two s, $C(C\underline{H}_3)_2$), 1.8—2.1 (2H, m, $ArCH_2C\underline{H}_2$), 2.4—3.15 (4H, m, $ArC\underline{H}_2$ ×2), 3.77 (6H, two s, $OC\underline{H}_3$ ×2), 4.09 (1H, q, $J$=6 Hz, $C\underline{H}CH_3$), 6.60 (2H, s, aromatic protons). *Anal.* Calcd for $C_{17}H_{24}O_4$: C, 69.84; H, 8.27. Found: C, 69.89; H, 8.37.

**Reduction of Optically Pure (*R*)-(−)- and (*S*)-(+)-2-Acetyl-5,8-dimethoxy-1,2,3,4-tetrahydro-2-naphthol ((*R*)-(−)- and (*S*)-(+)-3a) with Baker's Yeast**——Reduction of optically pure (*R*)-(−)-**3a** (mp 128—129 °C, $[\alpha]_D^{20}$ −46.6° ($c$=0.78, $CHCl_3$)) (100 mg, 0.40 mmol) with baker's yeast in the same manner as described for (±)-**3a** gave (−)-**4a** (47 mg, 47%), mp 153—154 °C, $[\alpha]_D^{20}$ −47.7° ($c$=0.64, EtOH), after extractive isolation followed by purification by PTLC ($SiO_2$, $C_6H_6$–EtOAc, 3.5:1). The spectral (IR and NMR) and chromatographic (TLC) properties of this

sample were identical with those of authentic (−)-**4a**. HPLC analysis showed that this sample consists solely of (−)-**4a**. The NMR spectrum of this sample exhibited a single doublet at 1.24 ppm ($J$=6 Hz) as expected for (−)-**4a**.

When (*S*)-(+)-**3a** (mp 128—129 °C, $[\alpha]_D^{20}$ +46.7° ($c$=0.51, $CHCl_3$)) (8 mg, 0.032 mmol) was reduced with baker's yeast in the same manner as described for (±)-**3a**, (+)-**5a** was obtained as a sole product (5.8 mg, 72%). HPLC analysis and the NMR spectrum of this sample showed that this sample was not contaminated with (+)-**4a**.

**(*R*)-(−)-2-Acetyl-5,8-dimethoxy-1,2,3,4-tetrahydro-2-naphthol ((*R*)-(−)-3a)**——Oxidation of (−)-**4a** (mp 154—155 °C, $[\alpha]_D^{20}$ −50.3° ($c$=0.66, EtOH)) (100 mg, 0.40 mmol) with DMSO–sulfur trioxide·pyridine complex–$Et_3N$ in the reported manner,[10b,28] followed by purification by PTLC ($SiO_2$, $C_6H_6$–EtOAc, 7:1), gave (*R*)-(−)-**3a** (90 mg, 90%), mp 126—127.5 °C, $[\alpha]_D^{20}$ −45.8° ($c$=0.90, $CHCl_3$). Recrystallization from $C_6H_{12}$ gave a pure sample, mp 128—128.5 °C, $[\alpha]_D^{20}$ −46.3° ($c$=0.54, $CHCl_3$) (lit.,[8b,c] mp 128—129 °C, $[\alpha]_D^{20}$ −48.6° ($c$=0.982, $CHCl_3$); lit.,[10] mp 128—129 °C, $[\alpha]_D^{20}$ −47.1° ($c$=1.11, $CHCl_3$)). The spectral (IR and NMR) properties of this sample were identical with those reported.[8c,10b] This sample showed no depression on mixed melting point measurement with authentic (*R*)-(−)-**3a**,[8b,c,10] mmp 128—129 °C.

**(*S*)-(+)-2-Acetyl-5,8-dimethoxy-1,2,3,4-tetrahydro-2-naphthol ((*S*)-(+)-3a)**——a) Preparation of (*S*)-(+)-**3a** from (+)-**5a**: Treatment of (+)-**5a** (mp 70—75 °C, $[\alpha]_D^{20}$ +41.1° ($c$=0.32, EtOH)) (28 mg, 0.11 mmol) as described for (−)-**4a** followed by purification by PTLC and three recrystallizations from $C_6H_{12}$, gave optically pure (*S*)-(+)-**3a** (11 mg, 40%), mp 128—129 °C, $[\alpha]_D^{20}$ +46.7° ($c$=0.51, $CHCl_3$). The IR and NMR spectra of this sample were identical with those of (*R*)-(−)-**3a**.

b) Preparation of (*S*)-(+)-**3a** from a Mixture of (−)-**4a** and (+)-**5a**: Crude mixture of (−)-**4a** and (+)-**5a** (18:82) (582 mg, 2.3 mmol) obtained from the reduction with baker's yeast was oxidized in the same manner as described for (−)-**4a**, affording partially optically active (*S*)-(+)-**3a** as a crystalline solid (417 mg, 72%) (42% from (±)-**3a**), mp 100—121 °C, $[\alpha]_D^{20}$ +30.2° ($c$=0.88, $CHCl_3$). The spectral (IR and NMR) properties of this sample were identical with those of optically pure (*R*)-(−)- and (*S*)-(+)-**3a**. The optical purity of this sample could be calculated as 65%ee since optically pure (*R*)-(−)-**3a** shows $[\alpha]_D^{20}$ −46.3° ($c$=0.54, $CHCl_3$). Based on this value, the ratio of (−)-**4a** to (+)-**5a** present in the starting material could be calculated as 18:82.

**5,8-Dimethoxy-2-tetralone (6a)**——A solution of $NaIO_4$ (34 mg, 0.16 mmol) in $H_2O$ (0.6 ml) was added to a solution of a mixture of (−)-**4a** and (+)-**5a** (mp 55—65 °C, $[\alpha]_D^{20}$ +24.4° ($c$=0.63, EtOH)) (20 mg, 0.079 mmol) in $Me_2CO$ (0.3 ml). After being stirred at room temperature for 1 h, the mixture was diluted with EtOAc and $H_2O$. The ethyl acetate layer was separated and washed successively with $H_2O$, satd. $NaHCO_3$, and $H_2O$. Filtration and concentration of the filtrate *in vacuo* gave **6a** as a crystalline solid (16.2 mg, 99%), mp 93—96 °C. Recrystallization from EtOH gave a pure sample, mp 98.5—99.5 °C (lit.,[10b] mp 98—99 °C; lit.,[27a] mp 98—99.5 °C).

**Racemization of Partially Optically Active (*S*)-(+)-2-Acetyl-5,8-dimethoxy-1,2,3,4-tetrahydro-2-naphthol ((*S*)-(+)-3a)**——Table I, Run 12: A solution of partially optically active (*S*)-(+)-**3a** (mp 100—121 °C, $[\alpha]_D^{20}$ +30.2° ($c$=0.88, $CHCl_3$, 65%ee)) (75 mg, 0.30 mmol) and TsOH–$H_2O$ (4.0 g, 21 mmol) in a mixture of $H_2O$ (2 ml) and AcOH (3.5 ml) was heated at 110 °C for 20 h under an argon atmosphere. After being cooled, the mixture was diluted with $H_2O$ and extracted with $CH_2Cl_2$. The combined organic extracts were washed successively with $H_2O$, satd. $NaHCO_3$, and $H_2O$. Filtration and concentration of the filtrate *in vacuo*, followed by purification by PTLC ($SiO_2$, $C_6H_6$–EtOAc, 6:1) afforded exclusively racemized (*S*)-(+)-**3a** as a solid (55.5 mg, 74%), $[\alpha]_D^{20}$ +3.9° ($c$=0.98, $CHCl_3$), 8%ee, 87% racemization (see Table I footnote *c*)). Recrystallization of a part of this sample (30 mg) from $C_6H_{12}$ gave (±)-**3a** (23.4 mg, 58%), mp 103—104 °C, $[\alpha]_D^{20}$ +0.6° ($c$=108, $CHCl_3$), 1%ee. The spectral (NMR) and chromatographic (TLC) behavior of this sample were identical with those of authentic (±)-**3a**.

**(±)-2-Acetyl-2,5,12-trihydroxy-1,2,3,4-tetrahydronaphthacene-6,11-dione ((±)-3c)**——A mixture of (±)-**3a** (5.0 g, 20 mmol), $AlCl_3$ (50 g, 0.38 mol), and NaCl (10 g) was heated at 180—185 °C for 3 min and worked up in a similar manner to that reported,[7b,e,10b,26a] to afford pure (±)-**3c** (5.2 g, 74%), after recrystallization from $CHCl_3$, mp 214—216 °C (lit.,[10b] mp 214—216 °C; lit.,[12] mp 202—203 °C; lit.,[24] 210—212 °C; lit.,[26a] mp 212—215 °C; lit.,[32b] mp 204—206 °C; lit.,[34] mp 160—162 °C; lit.,[35] mp 160—162 °C).

**(±)-2-Acetyl-2-hydroxy-5,12-dimethoxy-1,2,3,4-tetrahydronaphthacene-6,11-dione ((±)-3b)**——Methylation of (±)-**3c** by the reported procedure[10b] afforded (±)-**3b** in an almost quantitative yield. mp 186—188 °C (from MeOH) (lit.,[10b] mp 186—188 °C; lit.,[22a] mp 186—188 °C).

**Reduction of (±)-2-Acetyl-2-hydroxy-5,12-dimethoxy-1,2,3,4-tetrahydronaphthacene-6,11-dione ((±)-3b) with Baker's Yeast**——Preparation of (1′*S*,2*R*)-(−)-2-1′-Hydroxyethyl-2-hydroxy-5,12-dimethoxy-1,2,3,4-tetrahydronaphthacene-6,11-dione ((−)-**4b**) and Its (1′*S*,2*S*)-(+)-Isomer ((+)-**5b**): Baker's yeast (12.5 g) was added to a solution of sucrose (17.5 g) in $H_2O$ (150 ml), and the suspension was stirred at room temperature for 30 min. A DMSO solution (15 ml) of (±)-**3b** (98.5 mg, 0.26 mmol) was added to the aqueous suspension, and the whole was stirred at 25—30 °C for 17.7 h. Further sucrose (17.5 g) was added to the reaction mixture, and stirring was continued at 25—30 °C for 13.3 h (total 30 h). The reaction mixture was worked up as described in the case of the reduction of (±)-**3a**, giving an oily residue (0.51 g) after concentration of the ethyl acetate extract. Purification of the residue by column chromatography ($SiO_2$, $C_6H_6$–EtOAc, 1.5:1—1:1) afforded a mixture of (−)-**4b** and (+)-**5b** as a solid (90.3 mg, 91%), mp 153—165 °C, $[\alpha]_D^{20}$ −2.9° ($c$=0.86, DMF). The NMR spectrum of this sample showed two sets of doublets of an equal intensity at 1.13 and 1.16 ppm ($J$=each 6 Hz). This spectral feature suggests that almost equal

amounts of (−)-**4b** and (+)-**5b** are present in the crude mixture. Five recrystallizations of this sample from $C_6H_6$ gave pure (−)-**4b** (18.5 mg, 19% (38% based on (*R*)-(−)-**3b** present in (±)-**3b**)), mp 189—190 °C, $[\alpha]_D^{20}$ −39.0° (*c* = 0.66, DMF). IR $\nu_{max}^{KBr}$ $cm^{-1}$: 3340, 1665. NMR ($CDCl_3$) $\delta$: 1.13 (3H, d, *J* = 6 Hz, $CHC\underline{H}_3$), 1.6—2.0 (2H, m, $ArCH_2C\underline{H}_2$), 2.6—3.1 (4H, m, $ArC\underline{H}_2 \times 2$), 3.4—3.6 (1H, m, $C\underline{H}CH_3$), 3.79 and 3.81 (each 3H, two s, $OC\underline{H}_3 \times 2$), 4.19 (1H, s, $ArCH_2C(O\underline{H})$), 4.60 (1H, d, *J* = 6 Hz, $CH(O\underline{H})CH_3$), 7.65—7.90 and 7.90—8.10 (4H, two m, aromatic protons). MS *m/e*: 382 ($M^+$), 337 ($[M-45(CH_3CHOH)]^+$). *Anal.* Calcd for $C_{22}H_{22}O_6 \cdot 1/3H_2O$: C, 68.03; H, 5.88. Found: C, 68.28; H, 5.69.

Mother liquors from the repeated recrystallizations were combined and concentrated *in vacuo* to give a mixture of (−)-**4b** and (+)-**5b** (71 mg, 72%), mp 140—165 °C, $[\alpha]_D^{20}$ +9.2° (*c* = 1.76, DMF). The ratio of (−)-**4b** to (+)-**5b** could be calculated as 39 : 61, based on the optical purity of (*S*)-(+)-**3b** obtained from this sample. This solid was immediately used for oxidation or successive demethylation and oxidative cleavage of the *vicinal*-diol.

**Reduction of (*R*)-(−)-2-Acetyl-2-hydroxy-5,8-dimethoxy-1,2,3,4-tetrahydronaphthacene-6,11-dione ((*R*)-(−)-3b) with Baker's Yeast**——Reduction of (*R*)-(−)-**3b** (mp 140—141 °C, $[\alpha]_D^{20}$ −23.5° (*c* = 1.11, $CHCl_3$)) (40 mg, 0.11 mmol) with fermenting baker's yeast, followed by purification with PTLC ($SiO_2$, $C_6H_6$–EtOAc, 2 : 1), in the same manner as described for (±)-**3b**, gave (−)-**4b** as a reduction product (35.2 mg, 88%), mp 189—190 °C, $[\alpha]_D^{20}$ −35.0° (*c* = 0.65, DMF). The NMR spectrum of this sample exhibited a single doublet at 1.13 ppm (*J* = 6 Hz), suggesting that the reduction yields (−)-**4b** as a sole product. Recrystallization of this sample from $C_6H_6$ gave pure (−)-**4b**, mp 189—190 °C, $[\alpha]_D^{20}$ −38.5° (*c* = 0.58, DMF). This sample was identical with authentic (−)-**4c** on the basis of spectral (IR and NMR) and chromatographic (TLC) comparisons.

**(*R*)-(−)-2-Acetyl-2-hydroxy-5,12-dimethoxy-1,2,3,4-tetrahydronaphthacene-6,11-dione ((*R*)-(−)-3b)**——a) Preparation of Authentic (*R*)-(−)-**3b** from (*R*)-(−)-**3a**: Methylation of partially optically active (*R*)-(−)-**3c** (mp 195—200 °C, $[\alpha]_D^{20}$ −60.1° (*c* = 0.105, $CHCl_3$)) (198 mg, 0.56 mmol), prepared from (*R*)-(−)-**3a** (mp 128—129 °C, $[\alpha]_D^{20}$ −46.6° (*c* = 0.78, $CHCl_3$)) in the same manner as described for (±)-**3a**,[7b,e,10b,26a] with $Me_2SO_4$–$K_2CO_3$,[10b] gave crude (*R*)-(−)-**3b** (170 mg, 80%), mp 137—139 °C, $[\alpha]_D^{20}$ −22.9° (*c* = 1.60, $CHCl_3$). Recrystallization from $Et_2O$ afforded optically pure (*R*)-(−)-**3b** as yellow crystals (102 mg, 32% from (*R*)-(−)-**3a**), mp 140—141 °C, $[\alpha]_D^{20}$ −23.5° (c = 1.11, $CHCl_3$) (lit.,[10b] mp 140.5—141 °C, $[\alpha]_D^{20}$ −23.3° (*c* = 1.16, $CHCl_3$); lit.,[7a] mp 142—144 °C, $[\alpha]_D^{20}$ −32° (*c* = 1, $CHCl_3$)).

b) Preparation of (*R*)-(−)-**3b** from (−)-**4b**: A solution of sulfur trioxide·pyridine complex (47.9 mg, 0.30 mmol) in DMSO (0.15 ml) was added to a solution of (−)-**4b** (mp 189—190 °C, $[\alpha]_D^{20}$ −39.0° (*c* = 0.66, DMF) (11.5 mg, 0.030 mmol) and $Et_3N$ (91.3 mg, 0.90 mmol) in DMSO (0.075 ml), and the mixture was stirred at room temperature for 2 h. After being cooled, the mixture was diluted with dil. HCl (10% HCl (0.6 ml) + $H_2O$ (5 ml)) and extracted with $CHCl_3$. The combined extracts were washed with $H_2O$ and satd. NaCl. Filtration and concentration of the filtrate *in vacuo*, followed by purification by PTLC ($SiO_2$, $C_6H_6$–EtOAc, 6 : 1), gave (*R*)-(−)-**3b** as a yellow solid (9.8 mg, 86%), mp 139—140 °C, $[\alpha]_D^{20}$ −22.4° (*c* = 0.82, $CHCl_3$). Recrystallization from $Et_2O$ gave pure (*R*)-(−)-**3b** as yellow crystals, mp 140—140.5 °C, $[\alpha]_D^{20}$ −23.4 (*c* = 0.39, $CHCl_3$). This sample was identical with authentic (*R*)-(−)-**3b** prepared in a) on the basis of spectral (NMR) and chromatographic (TLC) comparisons and mixed melting point measurement, mmp 140—141 °C.

**(*S*)-(+)-2-Acetyl-2-hydroxy-5,8-dimethoxy-1,2,3,4-tetrahydronaphthacene-6,11-dione ((*S*)-(+)-3b)**——Oxidation of the crude mixture of (−)-**4b** and (+)-**5b** (mp 155—175 °C, $[\alpha]_D^{20}$ +9.2° (*c* = 1.76, DMF)) (33.4 mg, 0.087 mmol) in the same manner as described for (−)-**4b** gave partially optically active (*S*)-(+)-**3b** (29.2 g, 88%), mp 155—170 °C, $[\alpha]_D^{20}$ +5.2° (*c* = 1.22, $CHCl_3$), after purification by PTLC ($SiO_2$, $C_6H_6$–EtOAc, 6 : 1). The optical purity of this sample could be calculated as 22% ee, based on the assumption that (*R*)-(−)-**3b** showing $[\alpha]_D^{20}$ −23.5° (*c* = 1.11, $CHCl_3$) is optically pure. Therefore, the ratio of (−)-**4b** to (+)-**5b** in the starting material could be estimated as 39 : 61. The spectral (IR and NMR) properties of this sample were identical with those of (*R*)-(−)-**3b**.

**5,12-Dihydroxy-1,2,3,4-tetrahydronaphthacene-2,6,11-trione (6c)**——A crude mixture of (−)-**4b** and (+)-**5b** (mp 155—165 °C) (50 mg, 0.13 mmol), obtained from the reduction of (±)-**3b**, was added to a suspension of $AlCl_3$ (87 mg, 0.65 mmol) in $C_6H_6$ (15 ml), and the mixture was stirred at 50 °C for 2 h under an argon atmosphere.[10b,22] After being cooled, the mixture was diluted with 3% oxalic acid and extracted with EtOAc. The combined organic extracts were washed successively with $H_2O$, satd. $NaHCO_3$, $H_2O$, and satd. NaCl. Filtration and concentration of the filtrate *in vacuo* gave a crude mixture of (1′*S*,2*R*)- and (1′*S*,2*S*)-2-1′-hydroxyethyl-2,5,12-trihydroxy-1,2,3,4-tetrahydronaphthacene-6,11-dione (**4c** and **5c**) (38 mg, 82%), mp 195—205 °C. IR $\nu_{max}^{KBr}$ $cm^{-1}$: 3300, 1610, 1595. NMR ($CDCl_3$) $\delta$: 1.13 (3H, d, *J* = 6 Hz, $CHC\underline{H}_3$), 1.5—1.9 (2H, m, $ArCH_2C\underline{H}_2$), 2.5—3.0 (4H, m, $ArC\underline{H}_2 \times 2$), 3.4—3.7 (1H, m, $C\underline{H}(OH)$), 4.01 (1H, s, $O\underline{H}$), 4.5—4.7 (1H, m, $O\underline{H}$), 7.6—7.9 and 7.95—8.15 (4H, two m, aromatic protons), 13.19 and 13.21 (2H, two s, two phenolic $O\underline{H}$).

The mixture of **4c** and **5c** (20 mg, 0.066 mmol) was dissolved in a mixture of AcOH (1.5 ml) and $H_2O$ (0.75 ml) and $NaIO_4$ (12 mg, 0.056 mmol) was added to the acidic solution. After being stirred at −3—0 °C for 2.5 h, the reaction mixture was diluted with $CH_2Cl_2$ and $H_2O$, and the upper aqueous phase was separated. The upper aqueous layer was extracted with $CH_2Cl_2$, and the combined organic extracts were washed successively with $H_2O$, satd. $NaHCO_3$, and $H_2O$. Filtration and concentration of the filtrate *in vacuo*, followed by purification by column chromatography ($SiO_2$, $CH_2Cl_2$), afforded pure **6c** as a red powder (15 mg, 71% from the mixture of (−)-**4b** and (+)-

**5b**), mp >280 °C (lit.,[32b] mp >300 °C; lit.,[36] mp >310 °C; lit.,[37] mp >310 °C (decomp); lit.,[38] mp 296—298 °C). IR $\nu_{max}^{KBr}$ cm$^{-1}$: 1724, 1620, 1580. MS *m/e*: 382 ($M^+$).

**Racemization of Partially Optically Active (*S*)-(+)-2-Acetyl-2-hydroxy-5,8-dimethoxy-1,2,3,4-tetrahydronaphthacene-6,11-dione ((*S*)-(+)-3b)**——Heating of a solution of partially optically active (*S*)-(+)-**3b** (mp 183—188 °C, $[\alpha]_D^{20}$ +5.6° (*c*=1.15, $CHCl_3$), 24% ee) (21 mg, 0.060 mmol) and TsOH–$H_2O$ (735 mg, 3.9 mmol) in a mixture of $H_2O$ (0.37 ml) and AcOH (0.64 ml) at 110 °C for 20 h as described for (*S*)-(+)-**3a** gave crude racemized (*S*)-**3c** after extractive isolation. Methylation of this sample with $Me_2SO_4$–$K_2CO_3$ according to the reported method,[10b] followed by purification by PTLC ($SiO_2$, $C_6H_6$–EtOAc, 6:1), gave extensively racemized (*S*)-(+)-**3b** (14.8 mg, 70%), mp 160—180 °C, $[\alpha]_D^{20}$ +1.8° (*c*=1.20, $CHCl_3$), 8% ee, 68% racemization (see Table I footnote *c*)). Recrystallization of this sample from $C_6H_6$–$C_6H_{12}$ gave (±)-**3b** (10.6 mg, 50%), mp 184—186 °C, $[\alpha]_D^{20}$ +0.4° (*c*=0.79, $CHCl_3$), 2% ee. The spectral (NMR) and chromatographic (TLC) behavior of this sample were identical with those of authentic (±)-**3b**.

**(*R*)-(−)-2-Acetyl-2,5,12-trihydroxy-1,2,3,4-tetrahydroxynaphthacene-6,11-dione ((*R*)-(−)-3c)**——a) Preparation of (*R*)-(−)-**3c** from (*R*)-(−)-**3a**: Friedel–Crafts acylation of (*R*)-(−)-**3a** (mp 128—129 °C, $[\alpha]_D^{20}$ −46.6° (*c*=0.78, $CHCl_3$)) (98 mg, 0.39 mmol) in the same manner as described for (±)-**3a**[7b,e,10b,26a] gave partially optically active (*R*)-(−)-**3c** (104 mg, 75%), mp 206—209 °C, $[\alpha]_D^{20}$ −74.1° (*c*=0.108, $CHCl_3$), after extractive isolation and purification by column chromatography ($SiO_2$, $CH_2Cl_2$). Repeated recrystallizations from $C_6H_6$ gave optically pure (*R*)-(−)-**3c**, mp 218—219.5 °C, $[\alpha]_D^{20}$ −90.0° (*c*=0.106, $CHCl_3$) (lit.,[7b] mp 228—230 °C, $[\alpha]_D^{20}$ −87° (*c*=0.1, $CHCl_3$); lit.,[7e] mp 210—212 °C, $[\alpha]_D^{20}$ −84° (*c*=0.1, $CHCl_3$); lit.,[10b] mp 218—220 °C, $[\alpha]_D^{20}$ −87.0° (*c*=0.115, $CHCl_3$)).

b) Preparation of (*R*)-(−)-**3c** from (*R*)-(−)-**3b**: A mixture of (*R*)-(−)-**3b** (mp 140—141 °C, $[\alpha]_D^{20}$ −23.5° (*c*=1.11, $CHCl_3$)) (10 mg, 0.026 mmol) and $AlCl_3$ (17.5 mg, 0.13 mmol) in $C_6H_6$ (5 ml) was heated at 50 °C for 2 h with stirring under an argon atmosphere.[10b,22] After cooling, the mixture was diluted with 5% oxalic acid and extracted with $CHCl_3$. The organic extracts were combined, washed successively with $H_2O$, satd. $NaHCO_3$, and $H_2O$, filtered, then concentrated *in vacuo*. Purification of the residue by PTLC ($SiO_2$, $CH_2Cl_2$) afforded (*R*)-(−)-**3c** (7.5 mg, 81%), mp 214—216 °C, $[\alpha]_D^{20}$ −85.0° (*c*=0.110, $CHCl_3$). Recrystallization from $C_6H_6$ gave pure (*R*)-(−)-**3c**, mp 217—219 °C, $[\alpha]_D^{20}$ −89.5° (*c*=0.108, $CHCl_3$). This sample exhibited the same spectral (IR and NMR) and chromatographic (TLC) properties as (*R*)-(−)-**3c** obtained in a).

**Acknowledgements** The authors are grateful to Prof. Kenji Koga, Faculty of Pharmaceutical Sciences, University of Tokyo, for his encouragement and advice throughout this work.

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